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(54) **Sustained release pharmaceutical formulations.**

(57) The invention provides a sustained release formulation of ketoprofen comprising granules each of which comprises a core comprising ketoprofen and microcrystalline cellulose and a coating comprising awater-soluble and a water-insoluble cellulose derivative.

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SUSTAINED RELEASE PHARMACEUTICAL FORMULATIONS

This invention relates to a sustained release pharmaceutical composition containing ketoprofen, and to a method for its production

Ketoprofen [2-(3-benzoylphenyl)propionic acid] is a non-steroidal anti-inflammatory drug (NSAI) used in the treatment and control of a wide variety of conditions.

A number of formulations, including some sustained release, are known for this substance. Sustained release formulations are particularly suitable for NSAIs such as ketoprofen, as a single dose results in a therapeutic level of active material being maintained in the body for an extended period of time. There is however no generally applicable method for making such formulations and for each particular active material it is necessary to look at many criteria including rates of absorption, interactions with and between excipients, physical properties of active materials and of excipients, and bioavailability. Substantial experimentation must be undertaken in order to take into account such factors before a satisfactory formulation can be produced. It has now found that, by using a particular combination of excipients, a new, useful, sustained release formulation of ketoprofen can be produced.

The invention provides a sustained release formulation of ketoprofen, comprising granules, each of which comprises a core comprising ketoprofen and microcrystalline cellulose and a coating comprising a water-soluble and a water-insoluble cellulose derivative.

The preferred insoluble and soluble components are ethylcellulose (EC) and hydroxypropylmethylcellulose (HPMC) respectively.

The core is preferably made by extrusion and is preferably spherical in form (produced, for example, by spheronisation of an initially extruded body).

The proportion of ketoprofen to microcrystalline cellulose in the core is limited by the requirements of producing a stable core composition, capable of withstanding the coating process and any other necessary processing. There should also be sufficient ketoprofen present to limit the amounts of formulation to be administered to realistic levels. Ideally the amount of ketoprofen is 40 to 90, preferably 60 to 80, more preferably 75% (w/w).

A typical grade of microcrystalline cellulose that can be used is Avicel PH101.

The amount of coating applied is most readily defined in terms of the increase in weight of granules after coating. The preferred thickness depends on the precise nature of the coating and the required rate of release of the ketoprofen, but typically corresponds to a weight increase of 3 to 20,

preferably 5 to 15, more preferably 10%.

EC is insoluble in water and HPMC is water soluble. Therefore adjusting the relative proportions of the two coating materials will alter the rate at which the ketoprofen passes through the coating by varying the numbers and sizes of the pores which are created by the dissolution of the soluble component in the digestive tract. Clearly there must be sufficient of the insoluble component to retard drug release, but sufficient of the soluble component to allow passage of the ketoprofen through the coating at an acceptable rate after administration. Hence the ratio of the insoluble to soluble components must be tailored to the particular formulation.

Use of too high a proportion of the insoluble EC will result in very thin coatings being needed to obtain reasonable rates of release. This coating is then liable to be non-discrete and non-continuous, and there is also the possibility of significant variation of thickness. Hence there will be a lack of control of drug diffusion through the coating. On the other hand, the use of too high a proportion of the soluble HPMC will preclude adequate retardation of drug diffusion, even at very high coating thicknesses.

These factors provide practical limits to the coating composition. Bearing these factors in mind, typical levels of EC in the coating are in the range 95 to 50, preferably 90 to 60, more preferably 80 to 70% (w/w).

It is also preferred for the EC to have an ethoxy group content of 40-55%, more preferably 43-51% (by weight).

Typical grades of EC that can be used are Ethocel E7 and Ethocel E10 and of HPMC are Pharmacoat 606 and pharmacoat 615.

Conventional extra excipients, such as sodium carboxymethylcellulose, can be incorporated into the core during its formation. These typically account for less than 5% (w/w) of the core. Similarly, other conventional excipients can also be incorporated into the coating.

Typically the size of the granules is limited to a particular value or range, for example 0.5 to 2.0, preferably 0.8 to 1.4mm.

A further coating (for example an enteric coating, such as hydroxypropylmethylcellulose phthalate) can also be applied, in a conventional manner, to the particles according to the invention.

The particles according to the invention can be made by mixing ketoprofen and microcrystalline cellulose, optionally in the presence of further excipients (such as sodium carboxymethylcellulose) and optionally in the presence of sufficient water to

ensure adequate mixing and forming cores from this mixture, for example by extrusion and spheronisation. These are dried if necessary, and a suitable size fraction is isolated. This fraction is coated (for example in a fluidised bed) using a solution of a mixture of the two polymers in the desired proportions in a suitable solvent (for example a mixture of methanol and dichloromethane).

In-vitro tests show that formulations according to the invention do show an extended, approximately linear release rate for ketoprofen at typical physiological pH's, indicating that they are able to sustain a therapeutic level of ketoprofen in the body over a period of time.

The formulations according to the invention may be used in the management of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute articular and periaricular disorders (bursitis, capsulitis, synovitis, tendinitis), fibrositis, cervical spondylitis, low back pain (strain, lumbago, sciatica, fibrositis), painful musculo-skeletal conditions and dysmenorrhoea. They may be used, for example, to reduce joint pain and inflammation, and to facilitate increase in mobility and functional independence.

The typical daily dose for an adult would provide 50 to 500mg, more particularly 100 to 200mg, of ketoprofen, depending on the weight of the patient and the severity of the symptoms.

EXAMPLE

Ketoprofen (3kg) and microcrystalline cellulose (Avicel PH101; 965.6g) were thoroughly mixed in a planetary mixer. The resulting powder was granulated, over a period of 2 minutes, with a 1.5% (w/w) aqueous solution of sodium carboxymethylcellulose (Courlose) (2363g). The resulting mixture was extruded to produce cylindrical pieces, 1mm in diameter and 1mm or more long, which were spheronised by treatment for 3 minutes at 500rpm. The resultant spherical granules were dried at 40-50 °C for 17 hours and the 0.8-1.4mm fraction was separated out by sieving. The separated fraction was then coated with a freshly prepared 5% (w/w) solution of a 7:3(w/w) mixture of EC (Ethocel E7 Premium) and HPMC (Pharmacoat 606) in a 1:1 (w/w) mixture of methanol and dichloromethane to produce the final product.4

Claims

1. Granules, each of which comprises a core comprising ketoprofen and microcrystalline cellulose and a coating comprising a water-soluble and

a water-insoluble cellulose derivative.

2. Granules according to claim 1 in which the water-insoluble cellulose derivative is ethylcellulose and the water-soluble cellulose derivative is hydroxypropylmethylcellulose.

3. Granules according to claim 1 or 2 in which the amount of ketoprofen is 60 to 80 % w/w of the weight of microcrystalline cellulose in the core.

4. Granules according to any one of claims 1 to 3 in which the weight of the coating comprises 5 to 15 % of the weight of the core.

5. Granules according to any of claims 1 to 4 in which the coating comprises from 90 to 60 % w/w of ethylcellulose

6. Granules according to any one of the preceding claims which comprises as the water-insoluble cellulose derivative ethylcellulose having an ethoxy group content of 43 to 51 % by weight.

7. Granules according to any one of the preceding claims whose size is from 0.8 to 1.4 mm.

8. Granules according to any one of the preceding claims which comprise an enteric coating.

9. A process for the preparation of granules according to claim 1 which comprises mixing ketoprofen and microcrystalline cellulose, forming cores from the mixture obtained, if necessary drying the cores and isolating a desired size fraction, and forming on the cores a coating comprising a water-soluble and a water-insoluble cellulose derivative.

10. A pharmaceutical composition which comprises granules according to claim 1.



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EUROPEAN SEARCH REPORT

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 90401648.2
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Y	<u>EP - A1 - 0 313 328</u> (APS RESEARCH LIMITED) * Claims 1-4,9; page 6, lines 13-52; page 5, lines 3-13 * --	1,2,5, 7,9,10	A 61 K 31/19 A 61 K 9/24 A 61 K 9/36
Y	<u>GB - A - 1 568 837</u> (E.R. SQUIBB & SONS, INC.) * Claims 1,4; page 3, lines 88-91; example 1 * --	1,2,5, 7,9,10	
A	<u>GB - A - 2 190 287</u> (BIREX RESEARCH AND DEVELOPMENT LIMITED) * Claims 1,3,8 * --	1,3,8, 10	
A	<u>GB - A - 2 202 143</u> (EUROCELTIQUE S.A.) * Claims 1-3,6-9,14,17; example 3 * --	1,2,9, 10	
A	<u>GB - A - 2 025 227</u> (BOEHRINGER INGELHEIM) * Claims 1,11,15,16,26; example 1b * --	1,5,6, 10	TECHNICAL FIELDS SEARCHED (Int. Cl.) A 61 K 31/00 A 61 K 9/00
A	<u>US - A - 4 309 406</u> (P.C. GULEY et al.) * Claim 1; column 2, line 64 - column 3, line 2; example 6 * --	1,2,10	
A	<u>US - A - 4 385 078</u> (Y. ONDA et al.) * Abstract; claims 1,3,4 * --	1,2,10	
A	<u>EP - A1 - 0 148 811</u> (LEJUS MEDICAL AKTIEBOLAG) * Claims 1,3; page 3, lines 20-26 * --	1,2,10	
A	<u>US - A - 4 369 172</u> --	1,2,10	
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 17-09-1990	Examiner MAZZUCCO
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			



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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 8)
	(J.M. SCHOR et al.) * Abstract; claims 1,2,5; column 6, lines 11-18; column 7, lines 22-43 * -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 8)
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 17-09-1990	Examiner MAZZUCCO
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			